PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

Rec'd PCT/PTO 01 JUN 2005

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number: WO 00/06147
A61K 31/165, C07C 233/64	A1	(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/US99/17166

(22) International Filing Date: 30 July 1999 (30.07.99)

(30) Priority Data:

60/094,635	30 July 1998 (30.07.98)	US
60/095,059	3 August 1998 (03.08.98)	US

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: FRANZ, Robert, G. [US/US]; 169 Wildflower Drive, Plymouth Meeting, PA 19462 (US). GAITANOPOULOS, Dimitri, E. [US/US]; 1134 Bayless Place, Eagleville, PA 19403 (US). GIRARD, Gerald, R. [US/US]; 4741 Llanfair Place, Bensalem, PA 19020 (US). WEINSTOCK, Joseph, P. [US/US]; 10 Painters Lane, Wayne, PA 19087 (US).

(74) Agents: SIMON, Soma, G. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: MACROPHAGE SCAVENGER RECEPTOR ANTAGONISTS

(57) Abstract

Macrophage scavenger receptor antagonists are provided. Methods of treating cardiovascular disease comprising administration of the present compounds are also provided. The present compounds inhibit lipid accumulation within macrophage-derived foam cells.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

MACROPHAGE SCAVENGER RECEPTOR ANTAGONISTS

FIELD OF INVENTION

Cardiovascular diseases are the leading cause of death in the U.S., accounting annually for more than one million deaths. Atherosclerosis is the major contributor to coronary heart disease and a primary cause of non-accidental death in Western societies. Since the prevention of atherosclerosis is an enormous unmet medical need, considerable effort has been made in defining the etiology and potential treatment of atherosclerosis and its consequences, including myocardial infarction, angina, organ failure and stroke. Despite this effort, there are many unanswered questions including how and when atherosclerotic lesions become life-threatening, the best point of intervention, and how to detect and monitor the progression of lesions.

There is widespread agreement that multiple risk factors contribute to atherosclerosis including hypertension, elevated total serum cholesterol, high levels of low density lipoprotein ("LDL") cholesterol, low levels of high density lipoprotein ("HDL") cholesterol, diabetes mellitus, severe obesity, and cigarette smoking. To date, treatment of atherosclerosis has been narrowly focused on treating elevated cholesterol levels and modifying lipids has become the major focus of treatment and research.

However, recent studies have indicated that 40% of deaths due to coronary disease occurred in men with total cholesterol levels of below 220 mg/dl. It is thus obvious that too great an emphasis is being placed on lipid lowering. Indeed, only 30% of patients with atherosclerosis have elevated lipid levels, indicating that other pathogenic factors are involved. A logical scenario for future therapies and preventive measures should therefore include a multidisciplinary approach consisting of diet modification, HMG-CoA reductase inhibition and novel therapies aimed directly at plaque growth and stability.

The initial lesion in atherosclerosis is the fatty streak, which arises from cholesteryl esters maintained as lipid droplets inside macrophage-derived foam cells. Macrophages down-regulate their LDL receptors and instead express mRNA and undergo new protein synthesis for a novel receptor for modified LDL. This receptor recognizes all modified forms of low-density lipoprotein and has come to be known as the macrophage scavenger receptor ("MSR"). If the macrophage is present in an environment that is continually generating modified LDL, it will accumulate lipid droplets of cholosteryl esters, continuing until the macrophage dies from its toxic lipid burden. The released lipid then forms the

acellular necrotic core of the atherosclerotic lesion. Subsequent recruitment of fibroblasts, vascular smooth muscle cells and circulating monocytes and T-lymphocytes complete the inflammatory response and formation of the mature atherosclerotic plaque. Macrophage-derived foam cells are concentrated in the shoulders of plaques, where their secreted proteases and collagenases may contribute to plaque rupture which may lead to a fatal thrombotic event.

Plaque regression, a function of the dynamic balance among initiation, progression, stabilization and removal of plaque constituents, has been unequivocally demonstrated in humans as well as in numerous animal models. Multiple regression studies in non-human primates have shown that even relatively advanced lesions regress over time when atherogenic dietary stimuli are discontinued or pharmacological regimens are initiated.

Inhibition of lipid accumulation within macrophage-derived foam cells by utilizing MSR antagonists is expected to prevent plaque initiation, retard plaque progression, and initiate plaque regression through the process of "reversed cholesterol transport" to acceptor HDL. Thus, MSR antagonists provide a unique approach towards the pharmacotherapy of cardiovascular diseases such as atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, myocardial infarction, organ transplant, organ failure, and hypercholesterolemia.

SUMMARY OF THE INVENTION

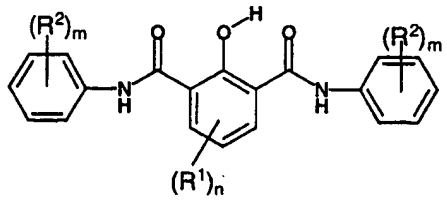
The present invention involves compounds represented by Formula (I) hereinbelow and their use as macrophage scavenger receptor ("MSR") antagonists which are useful in the treatment of a variety of cardiovascular diseases including but not limited to atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, stroke, myocardial infarction, organ transplant, organ failure and hypercholesterolemia.

The present invention further provides methods for antagonizing the macrophage scavenger receptor in animals, including humans, comprising administering to an animal in need of treatment an effective amount of a compound of Formula (I), indicated hereinbelow.

The present invention further provides methods of inhibiting lipid accumulation within macrophage-derived foam cells.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are selected from Formula (I) hereinbelow:



Formula (I)

wherein :

R^1 is independently selected from the group consisting of hydrogen, fluoroalkyl, halo, haloaryl, aryl, and alkoxy; or R^1 represents a fused ring forming a naphthalene moiety with the six membered aryl ring it substitutes;

R^2 is independently selected from the group consisting of hydrogen, R^1-benzamido, R^1-benzyl ether, R^1-benzylamino, amino, halo, hydroxy, alkoxy, alkyl, fluoroalkyl, cyano, nitro, aryloxy, nitroalkyl, aryl, and 1,2-benzo; or the R^2 moiety represents a fused ring forming a napthalene ring with the six membered aryl ring it substitutes;

m is an integer from 1 to 4; and

n is an integer from 1 to 3.

Preferably, R^1 is selected from the group consisting of hydrogen, 5-trifluoromethyl, 5-chloro, 5-bromo, 4-bromo, 5-bromo-4-phenyl, 5-iodo, 5-iodo-4-phenyl, 4-phenyl, 5-phenyl and 5-methoxy. More preferably, R^1 is hydrogen, 5-trifluoromethyl or 5-bromo.

Preferably, any R^2 aryl substituents are selected from the group consisting of hydroxy, halo, aryl, alkyl, cyano, nitro, R^1- benzamidyl, alkoxy and aryloxy. More preferably, R^2 is selected from the group consisting of 2-chloro, 3,4-dichloro, 2,3-dichloro, 3-methoxy, 2-isopropyl, 3-cyano, 4-butyl, 2-nitro, 2-phenoxy, 2-nitro-4-methyl, 2-phenyl, 4-phenyl, 2-benzamidyl, 1,2-benzo. Most preferably, R^2 is 3,4-dichloro, 4-bromo, 4-phenyl or 4-butyl.

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined together by single carbon-carbon bonds. Preferred alkyl substituents are as indicated throughout. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or

fused ring systems. "Aryl" includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. Preferred aryl substituents are as indicated throughout.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

Particularly preferred compounds useful in the present invention include: bis-N-(4-biphenyl)-5-bromo-2-hydroxyisophthalic dicarboxamide, bis-N-(4-biphenyl)-5-trifluoromethyl-2-hydroxyisophthalic dicarboxamide, and bis-N-(4-biphenyl)- 2-hydroxyisophthalic dicarboxamide, bis-N-(3,4-dichlorophenyl)-2-hydroxyisophthalic dicarboxamide, bis-N-(3,4-dichlorophenyl)-5-bromo-2-hydroxyisophthalic dicarboxamide, bis-N-(3,4-dichlorophenyl-2-hydroxy-5-trifluoromethylisophthalic dicarboxamide, bis-N-(4-bromophenyl)-5-bromo-2-hydroxyisophthalic dicarboxamide, bis-N-(4-bromophenyl)-2-hydroxyisophthalic dicarboxamide, and bis-N-(4-bromophenyl-2-hydroxy-5-trifluoromethylisophthalic dicarboxamide.

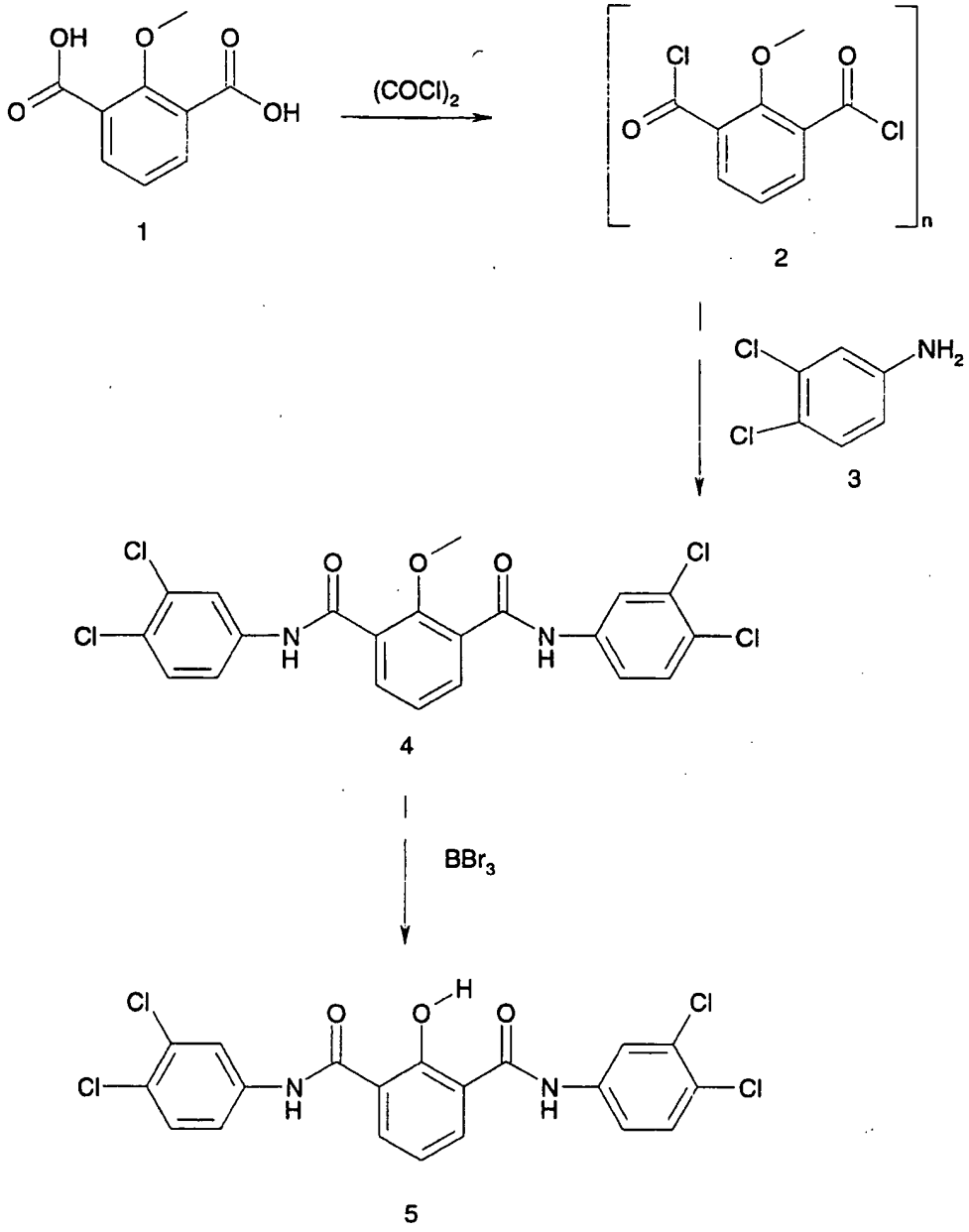
The present compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

Pharmaceutically acceptable salts for use when basic groups are present include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

The present invention provides compounds of Formula (I) above which can be prepared using standard techniques. An overall strategy for preparing preferred compounds described herein can be carried out as described in this section. The example which follows illustrates the synthesis of specific compounds. Using the protocols described herein as a model, one of ordinary skill in the art can readily produce other compounds of the present invention.

Scheme 1


OH
O
O
O
OH
(COCl)2
1
Cl
O
O
O
Cl
n
2
Cl
NH2
Cl
3
Cl
O
O
O
Cl
Cl
N
H
N
H
Cl
4
BBr3
H
5

Compound 1 is commercially available (Aldrich). The carboxylic acids can be activated towards condensation with amines by a variety of means. One of the most convenient is conversion to the bis-acid chlorides such as 2 by oxalyl chloride. Many other methods of making acid halides are well known as are procedures for preparing esters and especially activated esters. Many procedures are well known for the cleavage of aromatic methyl ethers including hydrohalic acids and nucleophiles such as sulfur and selenium compounds. An especially effective reagent is boron tribromide or an equivalent such as boron trichloride-sodium iodide.

Example 1

Bis-N,N'-(3,4-Dichlorophenyl)-2-hydroxyisophthalic dicarboxamide (5)

A suspension of 0.89 g (4.61 mmol) of 2-methoxyisophthalic acid in 25 ml of CH_2Cl_2 was treated with 4.68 g (36.8 mmol) of oxalyl chloride and a few drops of DMF. After 2.5 hr the reaction mixture was filtered, concentrated under vacuum, toluene added, and again concentrated under vacuum to a small volume. The residue was stirred with 150 ml of toluene and treated with 50 ml of a toluene solution containing 2.27 g (14 mmol) of 3,4-dichloroaniline and 3.2 ml (23.05 mmol) of triethylamine. After 18 hr. the reaction mixture was filtered and the collected solids washed with fresh toluene. The solid was dissolved in EtOAc, the organic solution washed with water and then brine, and dried over $MgSO_4$. Concentration under vacuum gave bis-N,N'-(3,4-dichlorophenyl)-2-methoxyisophthalic dicarboxamide (4) as a creamy white powder, mp 205-206C.

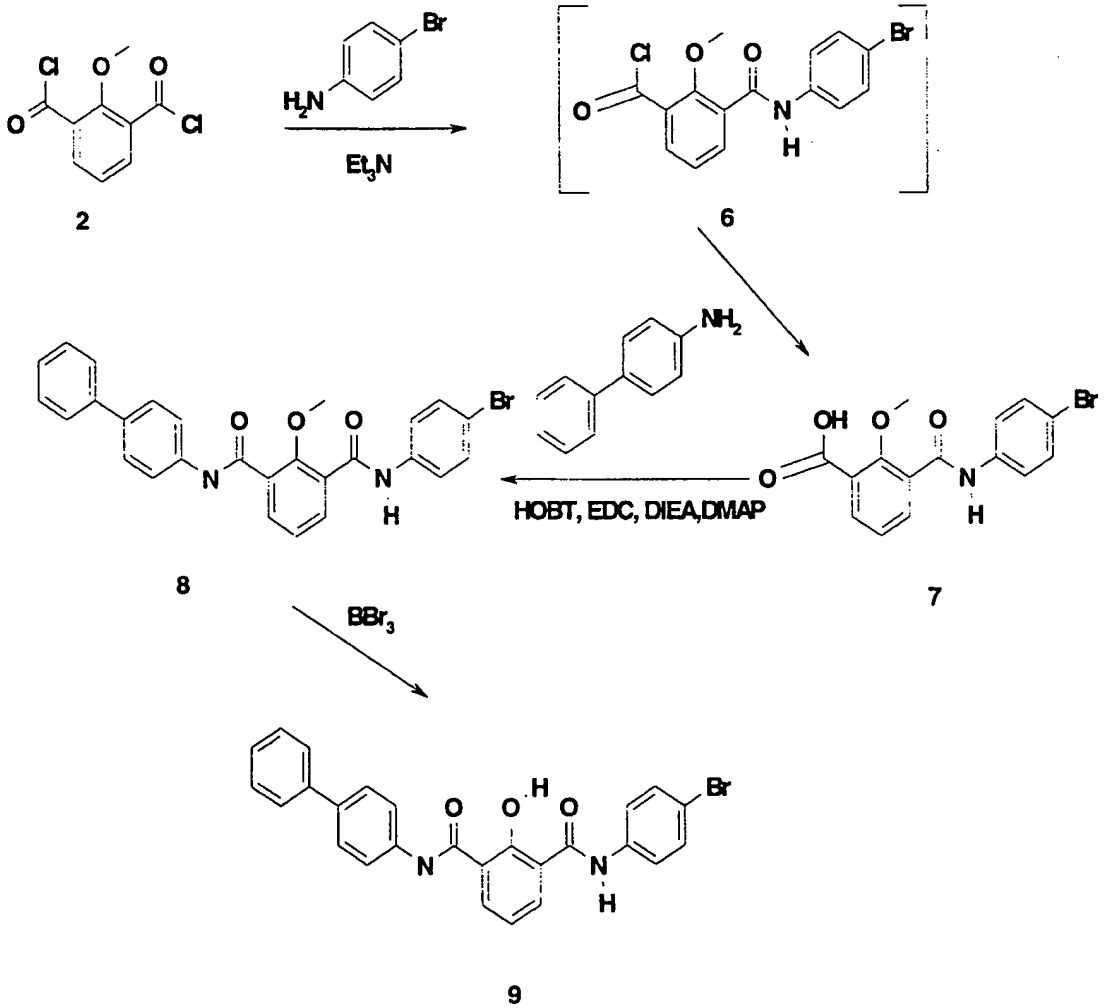
A suspension of 4 (250 mg, 0.52 mmol) in 25 ml of CH_2Cl_2 under argon was treated with 1.3 ml of a 1M solution of boron tribromide (1.3 mmol). After 4 hr 15 ml of MeOH was added and after 20 min concentrated under vacuum to give a solid which was recrystallized from toluene. This gave bis-N,N'-(3,4-dichlorophenyl)-2-hydroxyisophthalic dicarboxamide as straw yellow crystals, mp 232-235C.

By a similar procedure using 4-aminobiphenyl in place of 4, bis-N,N'-(4-biphenyl)-2-hydroxyisophthalic dicarboxamide, mp 200-202° C is obtained. Similarly using 4-bromoaniline in place of 4 gives bis-N,N'-(4 bromophenyl)-2-hydroxyisophthalic dicarboxamide mp 189-191°. Using 4-bromo-2-methoxy-isophthalic acid in place of 1 gives 4-bromo-bis-N,N'-(3,4-dichlorophenyl)-2-hydroxyisophthalic dicarboxamide, mp 292-295° C, 4-bromo-bis-N,N'-(4-bromophenyl)-2-hydroxyisophthalic dicarboxamide soften 169-170° C, mp 230-240°'and 4-bromo-bis-N,N'-(4-biphenyl)-2-hydroxyisophthalic dicarboxamide mp 216-219° C.. Using 4-trifluoromethyl-2-methoxy-isophthalic acid in

place of 1 gives 4-trifluoromethyl-bis-N,N'-(3,4-dichlorophenyl)-2-hydroxyisophthalic dicarboxamide, 4-trifluoromethyl-bis-N,N'-(4-bromophenyl)-2-hydroxyisophthalic dicarboxamide, and 4-trifluoromethyl-bis-N,N'-(4-biphenyl)-2-hydroxyisophthalic dicarboxamide. Other 2-methoxyisophthalic acids and anilines may also be used to give the corresponding anticipated products. Refluxing a mixture of 2,4-dihydroxyisophthalic acid, PCl_3, and 4-chloroaniline in chlorobenzene gives N,N'-bis-(4-chlorophenyl)-2,4-dihydroxyisophthalamide.

Unsymmetrical 2-hydroxyisophthalanilides may be made by stepwise reaction of 2-methoxyisophthalic diacid chloride to give a monoanilide, hydrolyzing the unreacted acid chloride, and then reacting the resulting acid with an aniline using standard amide forming reagents. Finally the methoxy group is cleaved to give the required 2-hydroxy derivative.

Scheme 2



Example 2

1-[N-(4-Bromophenyl)]-2-hydroxy-3-[N'-(4-biphenyl)]isophthalic dicarboxamide (**9**)

A solution of 0.44 g (2.6 mmol) of 4-bromoaniline and 0.36 ml (2.5 mmol) of triethylamine in 25 ml of dry toluene was added dropwise to a solution of 2-methoxyisophthalic diacid chloride 0.59 g (2.55 mmol) in 40 ml of toluene. After stirring for 18 hr at 25° C the volatiles were removed under vacuum and the residue dissolved in 30 ml of EtOAc. The solution was washed in turn with water, dil HCl, water, and 10% acqueous NaOH. Addition of HCl to bring the pH of the alkaline extract to 1 gave the monoanilide **7**, mp 193 – 196° C which had the anticipated MS.

A mixture of 0.35 g (1 mmol) of **9**, 0.148 g (1.1 mmol) of HOBT, 0.211 g (1.1 mmol) of EDC.HCl, and 0.38 ml (2.2 mmol) of DIEA in 1-methyl-2-pyrrolidinone was stirred at 25° for 0.5 h and then 0.22g (2.2 mmol) of 4-aminobiphenyl and 0.018 g (0.15 mmol) of DMAP added. After stirring at ambient for 18 hr the mixture was diluted with water, extracted with EtOAc and the extract washed with water, 10 % aqueous HCl, water, 5% Na_2C0_3, water, and brine. It was dried over $MgSO_4$, concentrated under vacuum, and the residue recrystallized from methanol to give **8**, mp 205-208°C.

A solution of 0.31 g (0.61 mmol) of **8** in 30 ml of CH_2Cl_2 was treated with a 1.0M solution of BBr_3 in CH_2Cl_2 (1.52 ml, 1.52 mmol) at 25°C for 18 hr. MeOH was added cautiously to decompose excess reagent, and then the solution was concentrated under vacuum to give a yellow residue which was dissolved in MeOH, filtered, concentrated under vacuum, and triturated with hexane to give a yellow solid. This was dissolved in CH_2Cl_2, filtered, and diluted with hexane to give a solid which was dissolved in $CHCl_3$ and filtered through a short silica column. Concentration gave **9**, mp 214-218°C which gave satisfactory elemental analyses for C, H, N, and Br.

A similar procedure gave 3-{N-(4-bromophenyl)]-1-[N-(3,4-dichlorophenyl)]-2-hydroxyisophthalic dicarboxamide, mp 218-220°C.

Example 3

N,N'-Bis-(4-chlorophenyl)-2,4-dihydroxyisophthalamide

A mixture of 0.4529 g (2.4 mmol) of 2,4-dihydroxyisophthalic acid, 0.62 g (4.84 mmol) of 4-chloroaniline, and 0.22 ml (2.2 mmol) of PCl_3 in 10 ml of chlorobenzene was refluxed for 3 hr. The hot reaction mixture was filtered and on cooling filtration gave the

desired product which on purification by preparative HPLC (C18, 20 – 95% acetonitrile - 0.1% aqueous TFA) gave saatisfactory elemental analyses for C,H, and N.

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The present compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and re-dissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the patient, and the disease

or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

The MSR receptors described in the present application belong to a recently classified group designated the SR-A group and exist in two forms, type A-I and type A-II, which arise through differential exon splicing of a single gene. The terms "MSR" and "SR-A" are used interchangeably in the present application.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia during clotting, stroke, organ transplant, organ failure, myocardial infarction and hypercholesterolemia.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used.

Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests.

Assays of MSR activity, both degradation and binding/internalization, were adapted from Goldstein et al., "Receptor-mediated Endocytosis of Low-density Lipoprotein in cultured Cells," *Methods Enzymol.*, 98:241-260 (1983); incorporated herein in its entirety by reference. Briefly, 293 cells transfected with MSRI or II are seeded at 10^5 cells/ml/well in a 24-well dish in Eagle's Minimal Essential Medium with 2 mM glutamine, 10% FCS and 0.4 mg/ml geneticin. After 2 days, the medium is replaced with 500µl fresh serum-free medium containing 2 mg/ml BSA and 125[I]-AcLDL (iodinated acetylated low density

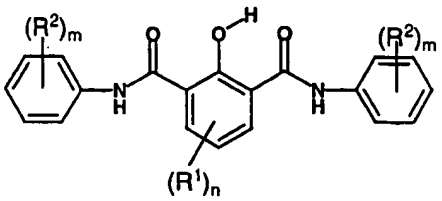
lipoprotein) at 5μg/ml, and cells are incubated at 37C for 5 hours. After this suitable period for ligand degradation, cells are removed to a 4C cold room. Supernatant is removed into trichloroacetic acid, and the mixture is centrifuged. The supernatant is chloroform-extracted in order to isolate 125[I]-monoiodotyrosine, the degradation product of 125[I]-AcLDL, and portions are counted to determine degradative activity. To determine cell-associated ligand, cell monolayers are washed and incubated at 4C with ice-cold buffer "A" containing 150 mM NaCl, 50 mM Tris-HCl, and 2 mg/ml BSA, pH 7.4, to eliminate nonspecifically bound counts. Cells are washed three times rapidly with 1 ml, incubated twice for 10 min each on a rotary shaker in 1 ml buffer A, then washed twice rapidly in 1 ml buffer A without BSA. After aspiration of all wash buffer, cells are lysed in 0.1N NaOH and removed to counting vials for determination of binding/uptake and subsequent protein determination (Pierce BCA protein assay). The present actives yield IC_{50} values of <50 um in degradation assays and <100um in binding/uptake assays.

The fluorescent compound DiI-AcLDL (1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate-labeled LDL) has also been shown to be a useful tool in assessing activity of the macrophage scavenger receptor (Freeman et al., *Proc. Natl. Acad. Sci., USA*, 88:4931-4935 (1991); Penman et al., *J. Biol. Chem.*, 266:23985-23993 (1991)). We also utilized an assay for MSR antagonists based on the uptake of DiI-AcLDL by the transfected HEK 293 cells. For most assays, HEK 293 cells transfected with SR-AI were used, although both SR-AI and SR-AII appeared to have equivalent activity in all studies performed. Briefly, HEK 293 cells were seeded at 2 x 10^4 cells/ well in a 96-well plate in EMEM with 2mM glutamine, 10%FBS and 0.4mg/ml geneticin. The assay was standardized and optimized, and testing was performed in serum-free EMEM containing 2mg/ml bovine serum albumin. Confluent cells were incubated with DiI-AcLDL (final concentration 2ug/ml) in the absence and presence of inhibitors (quadruplicate wells) for 4 hours at 37C. Following aspiration of solution and a Locke's buffer wash, results were quantified with a fluorescence plate reader at 530nm exc/590nm em.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A compound having the structure of Formula (I):



Formula (I)

wherein :

R^1 is independently selected from the group consisting of hydrogen, fluoroalkyl, halo, haloaryl, aryl, and alkoxy; or R^1 represents a fused ring forming a naphthalene moiety with the six membered aryl ring it substitutes;

R^2 is independently selected from the group consisting of hydrogen, R^1-benzamido, R^1-benzyl ether, R^1-benzylamino, amino, halo, hydroxy, alkoxy, alkyl, fluoroalkyl, cyano, nitro, aryloxy, nitroalkyl, aryl, and 1,2-benzo; or the R^2 moiety represents a fused ring forming a napthalene ring with the six membered aryl ring it substitutes;

m is an integer from 1 to 4; and

n is an integer from 1 to 3.

2. A compound according to claim 1 wherein:

R^1 is selected from the group consisting of hydrogen, 5-trifluoromethyl, 5-chloro, 5-bromo, 4-bromo, 5-iodo, 4-phenyl, 5-phenyl and 5-methoxy ; and

R^2 is selected from the group consisting of 2-chloro, 3,4-dichloro, 2,3-dichloro, 3-methoxy, 2-isopropyl, 3-cyano, 4-butyl, 2-nitro, 2-phenoxy, 2-nitro-4-methyl, 2-phenyl, 4-phenyl, 2-benzamidyl, 1,2-benzo.

3. A compound according to claim 2 wherein any R^2 aryl substituents are selected from the group consisting of hydrogen, hydroxy, halo, aryl, alkyl, cyano, nitro, R^1-benzamidyl, alkoxy and aryloxy.

4. A compound according to claim 3 wherein R^2 is selected from 3,4-dichloro, 2-benzamidyl, 4-bromo, 4-phenyl or 4-butyl.

5. A compound according to claim 4 wherein R^1 is hydrogen, 5-trifluoromethyl or 5-bromo.

6. A compound according to claim 5 wherein the compound is selected from the group consisting of:

bis-N-(4-biphenyl)-5-bromo-2-hydroxyisophthalic dicarboxamide, bis-N-(4-biphenyl)-5-trifluoromethyl-2-hydroxyisophthalic dicarboxamide, and bis-N-(4-biphenyl)- 2-

hydroxyisophthalic dicarboxamide, bis-N-(3,4-dichlorophenyl)-2-hydroxyisophthalic dicarboxamide, bis-N-(3,4-dichlorophenyl)-5-bromo-2-hydroxyisophthalic dicarboxamide, bis-N-(3,4-dichlorophenyl-2-hydroxy-5-trifluoromethylisophthalic dicarboxamide, bis-N-(4-bromophenyl)-5-bromo-2-hydroxyisophthalic dicarboxamide, bis-N-(4-bromophenyl)-2-hydroxyisophthalic dicarboxamide, bis-N-(4-bromophenyl-2-hydroxy-5-trifluoromethylisophthalic dicarboxamide.

7. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

8. A method of treating a cardiovascular disease or condition which comprises administering to a subject in need of treatment an effective amount of a compound according to claim 1.

9. A method according to claim 8 wherein the disease or disorder is selected from the group consisting of atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia due to clotting, organ transplant, organ failure, stroke, myocardial infarction and hypercholesterolemia.

10. A method according to claim 9 wherein the disease or disorder being treated is atherosclerosis.

11. A method of antagonizing a macrophage scavenger receptor comprising administering to a subject in need of treatment an effective amount of a compound according to claim 1.

12. A method of inhibiting lipid accumulation within macrophage-derived foam cells by administering to a subject in need of treatment an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
[redacted]S99/17166

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/165; C07C 233/64
US CL :564/164,165; 514/615
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/164,165; 514/615

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN EXPRESS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ------- Y,P	Database CAPLUS on STN (Columbus, OH, USA), No. 130:46650, Brooker et al.," Binuclear nickel (II) and copper (II) complexes of amide-containing two-armedand macrocyclic ligands " abstract, 30 November, 1998.	1
A	CH 459,172 A1 (WANDER et al.) 13 September 1968 (13.09.68) col. 30 (compound 102)	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 SEPTEMBER 1999	19 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE FAN Jerry J Dey for Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)★